

## ABSTRACT OF THE DISCLOSURE

The invention provides methods and compositions for modeling and detecting LDL receptor transmembrane signaling by detecting proteolysis of an LDL receptor transmembrane domain. The method comprises the steps of: a) providing a sample comprising a cell membrane comprising (i) a polypeptide comprising an LDL receptor transmembrane domain fused to a C-terminal tail, and (ii) a protease which specifically cleaves the domain and thereby releases the tail from the membrane; b) incubating the sample under conditions wherein the protease cleaves the domain and thereby releases the tail from the membrane; and c) detecting a resultant released tail.